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08/729,343	10/16/1996	DOSUK D. LEE		3866

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/729,343	LEE ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,9-16 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 7, 9-16, and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Continued Examination, Rule 132 Declaration, and Amendments/Remarks received 10/2/06 is acknowledged. Claims 1, 3, 7, 9-16, and 25 are pending in this application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by RE 33,221 to Brown et al.

Brown et al disclose a dental restorative cement pastes. The cements are used for conventional purposes, i.e. to fill a tooth socket, a replacement cone, a cement for implanting and replanting teeth, a material which promotes bone growth, bone implants or protheses. see column 9, lines 20-40. The composition is a mixture of two sparingly soluble calcium phosphates and a dilute aqueous solution. The calcium phosphate source is selected from amorphous, crystalline, or cryptocrystalline sources. The combination hardens into dental cement when contacted with living tissue. See abstract. The CaP mix contains tetracalcium phosphate and at least one sparingly soluble calcium phosphate, i.e. dicalcium phosphate dehydrate or brushite. See column 3, lines 35-50. The composition may be in a slurry, gel, cement, or injectable form. See example 3. Table II provides the instant setting times. Brown et al disclose methods of manipulating setting times by adding a sizable amount of hydroxyapatite seed crystals to the paste to facilitate

crystal formation. Further, crystal habit modifiers such as magnesium, citrates, or phosphonates may be used to promote expansion and adhesion. These modifiers absorb onto the specific sires of the crystal surfaces during growth affecting the morphology of the crystals. Further, appropriate combinations of varying particle sizes promote setting expansion. These modifiers includes Mg2+, Sr2+, citrate, phosphonates, carbonate, polyphosphates, sucrose phosphate and phosphocitrate. These modifiers absorb onto the specific sites of the crystal surfaces during growth, thereby affecting the morphology of the crystals. Additionally, appropriate combinations of varying or "gap-graded" particle sizes would promote setting expansion. See column 9, line 55 to column 10, line 5. Example 3 further teaches the manipulation of the setting time. The rate of remineralization may also be adjusted which affects the body's ability to resorb the material. Table 11 discloses the instant hardening time. Therefore rapid mineralization is beneficial under some circumstances such as incipient dental caries and lesions. Slow mineralization is beneficial for deep lesions. See column 8, lines 25-47.Brown discloses the instant composition is more porous and invaded by organic bone tissue (resorbable). see column 12, lines 40-50.

Response to Arguments and Rule 132 Declaration

Applicant argues that Brown teaches preparing a hydroxyapatite composition and not a PCA calcium phosphate. Applicant argues that Brown teaches the end product is a stoichiometric HA. Applicant argues that the Rule 132 states that there is a difference between the instant PCA calcium phosphate and Brown's hydroxyapatite. Dr. Strunk's in the Rule 132 declaration states that applicant's PCA calcium phosphate is a non-stoichiometeric calcium phosphate formed by incorporating carbonate ions into the crystal lattice, which increases its solubility and its

resorbability. Applicant argues that a vague teachings that the material is "bone-like" is not sufficient.

Applicant's arguments filed 10/2/06 have been fully considered but they are not persuasive. Firstly although the examiner notes applicant's arguments and the opinion Declaration state that PCA calcium phosphate contains carbonate, the examiner points out that the applicant is discussing natural bone and the instant claim is directed to synthetic PCA calcium phosphate. The examiner acknowledges that a term must be given its "plain meaning" unless it is inconsistent with the specification. MPEP 211.01. Although the applicant argues that the specification clearly defines PCA calcium phosphate contains carbonate and cites page 1, lines 19-27, the examiner points out that this page refers to natural bone.

The applicant specifically defines the instant PCA calcium phosphate on page 7 of the instant specification as:

> "Poorly crystalline apatitic calcium phosphate", "PCA calcium phosphate" and "PCA material", as those terms are used herein, describe a synthetic poorly crystalline apatitic calcium phosphate. The PCA material is not necessarily restricted to a single calcium phosphate phase provided it has the characteristic XRD and FTIR pattern. A PCA calcium phosphate has substantially the same X-ray diffraction spectrum as bone. Only two broad peaks in the region of 20-35° with one centered at 26° generally characterize the spectrum and the other centered at 32°. It is further characterized by FTIR peaks at 563 cm1, 1034 cm1, 1638 cm1 and 3432 cm1 (+ 2 cm-~). Sharp shoulders are observed at 603 cm~ and 875 cm-~, with a doublet having maxima at 1422 cm~ and 1457 cm-1.

Thus, in instance case the examiner must give weight to applicant's definition of the term since applicant provides a definition of the term. **Nowhere in the above definition does applicant require carbonate ions.** Although the examiner recognizes that natural PCA calcium phosphate contains carbonate ions, applicant's definition of synthetic PCA calcium phosphate does not.

Page 21 discloses:

> The PCA calcium phosphate of the invention is characterized by its biological resorbability, ability to promote bone ingrowth and substantial absence of crystallinity. Its crystalline character is substantially the same as natural bone, as compared to the higher degree of crystallinity seen in the bone substitute materials known to the art. The inventive PCA calcium phosphate also is biocompatible, that is, no significant detrimental reaction (e.g., inflammation or fibrosis) is induced in the host by the implanted composite material. Materials which induce a medically acceptable level of inflammation or fibrosis are considered biocompatible.

Again, applicant only discloses that the PCA calcium phosphate is similar to bone, it is resorbable and able to promote bone growth, and has low crystallinity. Again, applicant does not require carbonate as argued in the Rule 132 declaration and the arguments of 10/2/06. Thus, it is the examiner's position that Brown is considered to teach a PCA calcium phosphate in accordance to the above definition and disclosure.

Furthermore, the examiner notes that applicant incorporates US 5,650,176 to make the synthetic PCA calcium phosphate on page 16, 15-22. The instant specification discloses calcium phosphate is reacted to form PCA calcium phosphate wherein a crystalline inhibitor prevents full crystallization of PCA calcium phosphate (see page 18, lines 15-25). The crystallization inhibitors include carbonate, magnesium, and pyrophosphate.

Thus, in accordance with applicant's definition, it is the examiner's position that Brown discloses a PCA calcium phosphate implant. The examiner points out that Brown discloses the composition resorbable implant that hardens within the required time. Further, Brown teaches crystal modifiers including Mg2+, Sr2+, citrate, phosphonates, carbonate, polyphosphates, sucrose phosphate and phosphocitrate. Brown discloses that these modifiers absorb onto the specific sites of the crystal surfaces during growth, thereby affecting the morphology of the

crystals. Thus, Brown's material with the inclusion of the crystal modifier (as seen in the examples) would yield a *poorly crystallized product*; hence it is resorbable. The use of the term hydroxyapatite does not necessarily mean that the hydroxyapatite is in stoichiometric HA since HA exist in nonstoichiometric and stoichiometric form. The examiner cites US 6,214,368 to Lee et al (the instant inventor) as art of interest. US '368 teaches the method of making a *poorly crystalline hydroxyapatite calcium phosphate* implant. Clearly, using the term hydroxyapatite is not implicit that the hydroxyapatite in stoichiometric form as argued by applicant.

Lastly, it is noted that the Rule 132 declaration is a opinion declaration wherein applicant states that PCA calcium phosphate contains carbonate ions and is a nonstoichoimetric. This has been discussed above. The Declaration is not persuasive since the limitations in which applicant argues, are not claimed limitations.

Accordingly, the rejection is maintained.

Claims 1, 3, 7, and 9-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Constantz (5,962,028).

Constantz discloses a carbonated hydroxyapatite (HA) which is resorbable and a flowable mass that may be administered via a syringe and harden in situ. See abstract and column 4, line 33-35. The carbonated HA is non-stoichiometeric, i.e. poorly crystalline, wherein the Ca/P ratio is as low as 1.33. See column 4, lines 57-65. The composition ha a consistency of putty and may be molded prior to setting. Hardening usually takes at least about 5 minutes, more preferably at least about 15 minutes, and not more than about 20 minutes. See column 6, lines 25-45. The composition is administered at a physiological temperature of 37 degree C. see column 50-61. The composition is applicable as bone cements or fillers (reads on claim 11), dental or

endodontic fillers (reads on claim 10), coatings for bioimplantible substrates, or formed into a suitable shape before or after hardening into a monolithic structure (reads on claim 12). See column 8, lines 1-5.

With regard to the functional limitation of claim 1 and 9, i.e. the resorption rate, it is the examiner's position that since Constantz teaches the same product, the resorption rate will be inherent.

With regard to claim 7, although Constantz does not specify the x-ray pattern, it is the examiner's position that the prior art has the same differential pattern as that of instant invention since the Constantz teaches the same product, i.e. a poorly crystalline apatitic calcium phosphate. "Poorly crystalline apatite" as defined by the specification is at least one gram of PCA material is implanted, undergoes ossification in the body, and is resorbed.

Further, Constantz discloses the product is similar to native bone (see column 2) and natural bone contains carbonate; thus the prior art must have the same X-ray diffraction pattern.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz (5,962,028).

The teachings of Constantz have been delineated above. Constantz teaches the composition is applicable as bone cements or fillers, dental or endodontic fillers, coatings for bioimplantible substrates, or formed into a suitable shape before or after hardening into a monolithic structure. See column 8, lines 1-5.

Constantz does not specifically teach the instant implant sites.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Constantz and utilize the composition in the desired implant site. One would have been motivated to do so since Constantz teaches the instant composition as a variety of functions including a bone cements or fillers or formed into a suitable shape before or after hardening into a monolithic structure. Thus, depending on the area that required the composition, one would have been motivated to implant it at the given site. For instance, if one desired a bone filler for low density bone such as osteoporotic bone, one would have been motivated to fill osteoporotic bone.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz (5,962,028) in view of Ison et al (5,683,496).

The teachings of Constantz have been delineated above. Constantz teaches the composition comprises carbonate, acid phosphate source, and a calcium source such as tricalcium phosphate, tetracalcium phosphate, etc. The composition is made by reacting an acidic

phosphate source and a basic calcium source. Example 2 teaches a composition comprising monobasic calcium phosphate monohydrate(acidic phosphate source), tetracalcium phosphate (calcium source), calcium carbonate, calcium oxide, and orthophosphoric acid. Note that the carbonate causes the calcium phosphate to be poorly crystallized.

Constantz does not teach the use of amorphous calcium phosphate as the calcium source to make the carbonated hydroxyapatite.

Ison teaches storage stable calcium phosphate cement. The cement is a moldable paste that is applied to the bone site to provide a bone-like structure. See column 1, lines 30-45. Ison teaches the calcium phosphate ratio depends on the type of cement desired. If a carbonated hydroxyapatite is desired, a cement having a Ca/P ratio is 1.33 to 2. The composition is made by reacting an acidic phosphate source and a basic calcium source. See column 3-4. The calcium source is selected from tetracalcium phosphate, tricalcium phosphate, or amorphous calcium phosphate and the acidic phosphate source may be monobasic calcium phosphate monohydrate. See column 3, lines 15-55.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Constantz '028 and Ison and utilize amorphous calcium phosphate as the calcium source. One would have been motivated to do so since Ison teaches the equivalency of tricalcium phosphate, tetracalcium phosphate, and amorphous calcium phosphate, as the calcium source in making a carbonated hydroxyapatite implant.

Claims 1, 3, 7, 9-16, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/02412 to Simkiss et al.

Simkiss et al teach an amorphous calcium phosphate mixed with a crystal inhibitor that hardens to form bone in vivo. See abstract. A mixture of amorphous calcium phosphates may be used with different transformation rates wherein amount of the inhibitor effects the crystallinity of the material. See page 6. The precursor material is applied to the site where bone growth is required. See page 3. Simkiss teaches hydroxyapatite Ca5(OH)PO4)3 on page 1 as the inorganic material of choice. The molar ratio of Ca to P is 1.67. Tricalcium phosphate is also taught which has a molar ratio of 1.5. Negligible amounts of magnesium in the composition (as low as 0.001 moles for 1 mole calcium). It should be noted that compositions containing hydroxyapatite or tricalcium phosphate having magnesium and tricalcium phosphate are known to be resorbable and are not poorly crystalline since the magnesium prevents full crytallization. Simkiss exemplifies a material wherein the material is hardened after "many hours". See page 4. However, Simkiss also teaches the ability to modify the transformation rates when the material is exposed to body fluid, by including crystallization inhibitors such as pyrophosphate or magnesium ions in certain proportions. See page 2, last paragraph. Simkiss teaches the precursor material contains the inhibitors in low levels, which inhibit the crystallization of the material, and when the implant is in vivo, the inhibitors are leached away by body fluid, thus causing the precursor material to undergo transformation into crystalline hydroxyapatite. See page 3. On page 6, Simkiss teaches transformation time can be controlled by the choice of inhibitor and the choice of inhibitor concentration and/or solubility. A slow mechanism is taught as one requiring natural bone formation and repair mechanism. However, fast-setting material may be used depending on the intended use such as bone filling or bone-grafting. See page 6. X-ray diffraction patterns are seen in Figure 1.

Simkiss does not teach the recited setting time.

However, it is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Simkiss and formulate a fast-setting precursor material. One would have been motivated so depending on the intended use of the implant. For instance, Simkiss teaches the use of fast setting for uses such as bone filling whereas if natural bone formation is desired, one would utilize a slow-setting material. Therefore, the motivation to manipulate the parameters of the prior art depends on the intended use of the implant and treatment plan. Furthermore, Simkiss provides guidance on how to formulate the desired setting rate by stating that a higher concentration of crystallization inhibitor provides for a slow-rate and less of the inhibitor provides for a fast rate. It should be further noted that the instant claims recite "hardened within..." but do not recite the degree of hardness. For instance, Simkiss exemplifies a product that takes hours to completely hardened, however the start of the hardening process could fall within applicant's range. Lastly, it should be noted that it is the examiner's position that since Simkiss teaches similar precursor material without distinction, the functional limitation, i.e. the resorption rate will be implicit. However, if applicant argues otherwise, then the applicant has the burden of proving otherwise.

Response to Arguments and Rule 132 Declaration

Applicant argues that Simkiss does not teach a poorly crystalline apatite (PCA) calcium phosphate. Applicant argues that Simkiss teaches the use of stoichiometric crystalline hydroxyapatite (HA). Applicant argues that the Rule 132 states that there is a difference between the instant PCA calcium phosphate and Simkiss's hydroxyapatite. Dr. Strunk's in the Rule 132 declaration states that applicant's PCA calcium phosphate is a non-stoichiometeric calcium

phosphate formed by incorporating carbonate ions into the crystal lattice, which increases its solubility and its resorbability. Applicant argues that Simkiss's pre-product takes hours to harden and requires the removal of inhibitor ions by leaching for it to harden. Applicant argues once it hardens, it forms a stoichiometric crystalline hydroxyapatite.

Applicant's arguments filed 10/2/06 have been fully considered but they are not persuasive. Firstly although the examiner notes applicant's arguments and the opinion Declaration state that PCA calcium phosphate contains carbonate, the examiner points out that the applicant is discussing natural bone and the instant claim is directed to synthetic PCA calcium phosphate. The examiner acknowledges that a term must be given its "plain meaning" unless it is inconsistent with the specification. MPEP 211.01. Although the applicant argues that the specification clearly defines PCA calcium phosphate contains carbonate and cites page 1, lines 19-27, the examiner points out that this page refers to natural bone.

The applicant specifically defines the instant PCA calcium phosphate on page 7 of the instant specification as:

> "Poorly crystalline apatitic calcium phosphate", "PCA calcium phosphate" and "PCA material", as those terms are used herein, describe a synthetic poorly crystalline apatitic calcium phosphate. The PCA material is not necessarily restricted to a single calcium phosphate phase provided it has the characteristic XRD and FTIR pattern. A PCA calcium phosphate has substantially the same X-ray diffraction spectrum as bone. Only two broad peaks in the region of 20-35° with one centered at 26° generally characterize the spectrum and the other centered at 32°. It is further characterized by FTIR peaks at 563 cm1, 1034 cm1, 1638 cm1 and 3432 cm1 (+ 2 cm-~). Sharp shoulders are observed at 603 cm~ and 875 cm-~, with a doublet having maxima at 1422 cm~ and 1457 cm-1.

Thus, in instance case the examiner must give weight to applicant's definition of the term since applicant provides a definition of the term. **Nowhere in the above definition does applicant require carbonate ions.** Although the examiner recognizes that natural PCA calcium

phosphate contains carbonate ions, applicant's definition of synthetic PCA calcium phosphate does not.

Page 21 discloses:

> The PCA calcium phosphate of the invention is characterized by its biological resorbability, ability to promote bone ingrowth and substantial absence of crystallinity. Its crystalline character is substantially the same as natural bone, as compared to the higher degree of crystallinity seen in the bone substitute materials known to the art. The inventive PCA calcium phosphate also is biocompatible, that is, no significant detrimental reaction (e.g., inflammation or fibrosis) is induced in the host by the implanted composite material. Materials which induce a medically acceptable level of inflammation or fibrosis are considered biocompatible.

Again, applicant only discloses that the PCA calcium phosphate is similar to bone, it is resorbable and able to promote bone growth, and has low crystallinity. Again, applicant does not require carbonate as argued in the Rule 132 declaration and the arguments of 10/2/06. Thus, it is the examiner's position that Brown is considered to teach a PCA calcium phosphate in accordance to the above definition and disclosure.

Thus, it is the examiner's position that Simkiss is considered to teach a PCA calcium phosphate in accordance to the above definition and disclosure. The examiner points out that Simkiss teaches the material has similar peaks as seen on Figure 1 herein a broad peak is noted at 26° and at 32°. The Rule 132 declaration states that Simkiss does not teach a peak at 28°. Firstly, the independent claim does not require this. Secondly, the examiner notes that instant Figure 3c and Simkiss' Figure 1 are similar wherein there is a slight peak at about 28°. Moreover, Simkiss teaches the material is restorable and encourages natural bone growth. This is in accordance to applicant's disclosure of the properties of PCA calcium phosphate.

Furthermore, the examiner notes that applicant incorporates US 5,650,176 to make the synthetic PCA calcium phosphate on page 16, 15-22. The instant specification discloses that amorphous calcium phosphate is reacted to form PCA calcium phosphate wherein a crystalline inhibitor prevents full crystallization of PCA calcium phosphate (see page 18, lines 15-25). The crystallization inhibitors include carbonate, magnesium, and pyrophosphate.

Simkiss teaches using a crystallization inhibitor such as magnesium with the amorphous calcium phosphate to prevent complete crystallization of the amorphous calcium phosphate. Thus, Simkiss' material is not completely crystallized as argued since it contains a crystallization inhibitor. Therefore, the material also cannot be in stoichiometric proportion.

Applicant argues that the magnesium phosphate leaches to provide a stoichiometric hydroxyapatite. Firstly, the examiner points out that applicant's method does not exclude this leaching process. Secondly, the examiner points out that although Simkiss states that this leaching process provides for a crystalline HA, nowhere does Simkiss state that this crystallized HA is fully crystallized in stoichiometric proportion. The use of the term hydroxyapatite does not necessarily mean that the hydroxyapatite is in stoichiometric HA since HA exist in nonstoichiometric and stoichiometric form. The examiner cites US 6,214,368 to Lee et al (the instant inventor) as art of interest. US '368 teaches the method of making a poorly crystalline hydroxyapatite calcium phosphate implant. Clearly, using the term hydroxyapatite is not implicit that the hydroxyapatite in stoichiometric form as argued by applicant. The fact that Simkiss states that it has transformed from the amorphous state to the crystalline state does not mean that is has fully crystallized, i.e. it may be crystallized compared to an amorphous calcium phosphate but it many be poorly crystallized. The examiner position is further substantiated by the Figure 1

in Simkiss. Figure 1 provides the X-ray diffraction pattern after the leaching process has take place. Figure 1 has peaks similar to applicant's X-ray diffraction pattern. Lastly, the examiner points out that if arguendo applicant's synthetic PCA calcium phosphate contained carbonate ions, it too would leach out and undergo the same process since it too is a crystalline inhibitor that is soluble in physiological medium.

Applicant argues that Simkiss provides the X-ray diffraction pattern of natural bone and not the synthetic material. The examiner notes page 4 of Simkiss. However, Simkiss clearly states that "similar experiments were carried out with the synthetic samples as specified at (2). It was found that the time taken to effect transformation varied with the concentration of magnesium, in the sample. Thus, it is the examiner's position that this is an implicit teachings that the only difference between the naturally derived material and synthetic material was the transformation timing and not the X-ray diffraction pattern. Thus, only one X-ray diffraction pattern is provided. When Simkiss notes the differences between the naturally derived material and the synthetic material, Simkiss does not teach that the materials had different X-ray diffraction patterns.

Lastly, it is noted that the Rule 132 declaration is a opinion declaration wherein applicant states that PCA calcium phosphate contains carbonate ions and is a nonstoichoimetric. This has been discussed above. The Declaration is not persuasive since the limitations in which applicant argues, are not claimed limitations.

Accordingly, it is the examiner's position that Simkiss renders the instant invention obvious.

The rejection of claims 1, 3, 7, 9-16, and 25 under 35 U.S.C. 103(a) as being unpatentable over WO 94/02412 to Simkiss et al by itself or in view of RE 33,221 to Brown et al is maintained.

Simkiss et al teach an amorphous calcium phosphate that hardens to form bone in vivo. See abstract. The precursor material is applied to the site where bone growth is required. See page 3. Simkiss teaches hydroxyapatite Ca5(OH)PO4)3 on page 1 as the inorganic material of choice. The molar ratio of Ca to P is 1.67. Tricalcium phosphate is also taught which has a molar ratio of 1.5. Negligible amounts of magnesium in the composition (as low as 0.001 moles for 1 mole calcium). It should be noted that compositions containing hydroxyapatite or tricalcium phosphate having magnesium and tricalcium phosphate are known to be resorbable. Simkiss exemplifies a material wherein the material is hardened after "many hours". See page 4. However, Simkiss also teaches the ability to modify the transformation rates when the material Is exposed to body fluid, by including crystallization inhibitors such as pyrophosphate or magnesium ions in certain proportions. See page 2, last paragraph. Simkiss teaches the precursor material contains the inhibitors in low levels, which inhibit the crystallization of the material, and when the implant is in vivo, the inhibitors are leached away by body fluid, thus causing the precursor material to undergo transformation into crystalline hydroxyapatite. See page 3. On page 6, Simkiss teaches transformation time can be controlled by the choice of inhibitor and the choice of inhibitor concentration and/or solubility. A slow mechanism is taught is one required natural bone formation and repair mechanism. However, fast-setting material may be used depending on the intended use such as bone filling or bone-grafting. See page 6. X-ray diffraction patterns are seen in Figure 1.

Simkiss does not teach the recited setting time.

Brown et al disclose dental restorative cement pastes. The cements are used for conventional purposes, i.e. to fill a tooth socket, a replacement cone, a cement for implanting and replanting teeth, a material which promotes bone growth, etc. see column 9, lines 20-40. The composition is a mixture of two sparingly soluble calcium phosphates and a dilute aqueous solution. The combination hardens into dental cement when contacted with living tissue. See abstract. The CaP mix contains tetracalcium phosphate and at least one sparingly soluble calcium phosphate, i.e. dicalcium phosphate dehydrate or brushite. See column 3, lines 35-50. The composition may be in a slurry, gel, cement, or injectable form. See example 3. Table II provides the instant setting times. Brown et al disclose methods of manipulating setting times by adding a sizable amount of hydroxyapatite seed crystals to the paste to facilitate crystal formation. Further, crystal habit modifiers (up to 1%) such as magnesium, citrates, or phosphonates may be used to promote expansion and adhesion. These modifiers absorb onto the specific sites of the crystal surfaces during growth affecting the morphology of the crystals. Further, appropriate combinations of varying particle sizes promote setting expansion. See column 9, line 55 to column 10, line 5. Example 3 further teaches the manipulation of the setting time. The rate of remineralization may also be adjusted which affects the body's ability to resorb the material. Therefore rapid mineralization is beneficial under some circumstances such as incipient dental caries and lesions. Slow mineralization is beneficial for deep lesions. See column 8, lines 25-47.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Simkiss et al and Brown et al and manipulate Simkiss's formulation to yield a fast-setting precursor material. One would have been motivated so since

Brown et al also teach a calcium phosphate injectable composition that has setting capabilities at physiological temperatures. Further, Brown provides guidance on how to manipulate the setting condition by changing the amount of hydroxyapatite, adding crystal modifiers such as magnesium, phosphonates, and citrates, which also taught by Simkiss for the same purpose of manipulating setting time. Therefore, it can be seen that manipulation of setting times is a conventional practice done in the art at the time the invention was made. Lastly, one would have been motivated to manipulate the parameters of the prior art depending on the intended use of the implant and treatment plan as taught by both Simkiss and Brown et al.

Response to Arguments

Applicant argues that Simkiss and Brown do not teach or suggest the preparation of a PCA calcium phosphate for use of treating a bone defect or embedding a prosthesis. Applicant argues that both Simkiss and Brown teach preparing a hydroxyapatite composition and thus all the limitations of the claims are not met.

Applicant's arguments filed 10/2/06 have been fully considered but they are not persuasive. The merits of Brown and Simkiss have been discussed above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 1, 3, 7, 9-16, and 25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,214,368, claims 1-2 of U.S. Patent No. 6,132,463, claims 1-21 of U.S. Patent No. 6,027,742, claims 1-9 of U.S. Patent No. 6,331,312 are maintained for the reasons set forth in the Office Action of April 23, 2003.

Response to Arguments

Applicant states that upon allowance of the instant claims, the applicant may consider filing of a Terminal Disclaimer to overcome the rejection. Accordingly, the rejection is maintained.

Claims 1, 3, 7, 9-16, and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-55 of U.S. Patent No. 6,541,037, claims 12-19 and 21 of U.S. Patent No. 6,214,368, claims 1-27 of U.S. Patent No. 6,277,151.

The instant application id directed to a method of treating a bone defect by providing a resorbable PCA calcium phosphate that is injectable and hardened within 10-60 minutes. At least 80% is resorbed in one year. Claim 25 is directed to a method of prosthetic device by applying a paste comprising amorphous calcium phosphate, PCA calcium phosphate, and a fluid wherein hardened within 10-60 minutes.

US '037 is directed to a method of delivering a active agent comprising providing a paste composition with an injectable consistency comprising amorphous calcium phosphate, an acidic

calcium phosphate (selected from claim 42 including instant PCA calcium phosphate), and solution wherein the composition is applied and allowed to harden with an endothermic process. The same Ca/P ratio is claimed; the same hardening time is claimed, and the same resorption rate is claimed.

US '368 is directed to a method of promoting bone growth, comprising: providing a paste, said paste comprising a calcium phosphate powder, said powder comprising a first calcium phosphate material having at least 90% amorphous character and an acidic second calcium phosphate material (selected from claim 19 including instant PCA calcium phosphate), the powder having a calcium to phosphorous molar ratio in the range of about 1.2 to 1.68, and a fluid in an amount which provides a formable or injectable consistency, said paste remaining injectable or formable for a time greater than about 60 minutes at about 22.degree. C.; applying the paste to a site requiring bone growth: and allowing the paste to harden at the site within about 30 minutes. It is the examiner's position that the composition would have the same functional limitations as the instant composition since both compositions are the same.

US '151 is directed to a method of growing collagen in vivo comprising hydrating a composition into a site comprising a amorphous calcium phosphate, a precursor (selected from claim 10 including instant PCA calcium phosphate), and a solution. The ACP is converted into a PCA calcium phosphate. The same Ca/P ratio is claimed and the same hardening time is claimed. It is the examiner's position that the composition would have the same functional limitations as the instant composition since both compositions are the same.

Accordingly, instant application and US patents are directed to similar subject matter. It is noted that although the US patents does not claim the specific implant site as claimed in claims

10-16, this is a obvious parameter wherein it is known to implant a substitute bone composition in the area that requires the implant.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila S. Gollamudi
Examiner
Art Unit 1616